REMARKS

Claims 42, 44-51, 54, 58, and 64-78 are pending in this application. Claims 42, 66, 76, and 78 are amended. Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 42, 44-51, 54, 58, and 64-78 in condition for allowance. The amendments merely clarify the language of the claims in response to concerns raised by the Examiner. Applicants submit that the proposed amendments of claims 42, 66, 76, and 78 do not add new matter, raise new issues, or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

35 U.S.C. §112, second paragraph

Claim 78 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite due to recitation of "neural progenitors." Applicants have amended claim 78 to recite "neural progenitor cells," thus rendering the rejection moot.

35 U.S.C. §112, first paragraph

Claims 42, 44-51, 54, 58, and 64-78 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. Specifically, the Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse.

The method of Claim 42 is directed to purification or enrichment of a cell culture for neural progenitor cells in which a pluripotent cell is first modified to introduce a

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selectable marker. Expression of this selectable marker is under the control of a Sox gene promoter. As a result, the selectable marker will be expressed in neural progenitor cells at a higher level than it is in other cells, where the marker is expressed at very low levels -- or not at all.

Next, the modified pluripotent cell is cultured *in vitro* under conditions that induce differentiation of the pluripotent cell into neural progenitor cells or a mixed population of cells including neural progenitor cells. Neural progenitor cells are then purified from the culture or the culture is enriched for neural progenitor cells by applying selection. For example, if the selectable marker used to modify the pluripotent cells is an antibiotic resistance gene, addition of an appropriate antibiotic to the culture medium would result in the selective killing of cells in which the selectable marker is not expressed. Neural progenitor cells, in which the selectable marker is differentially expressed under the control of a Sox gene promoter, would not be killed on exposure to the antibiotic.

The method of claim 66 involves equivalent steps. However, differential expression of the selectable marker in neural progenitor cells is achieved by introducing into a pluripotent cell a selectable marker under the control of a promoter of a gene that is differentially expressed in neural progenitor cells. The modified pluripotent cell is then cultured *in vitro* to induce differentiation, resulting in a population of cells that includes neural progenitor cells and cells of other types. Selection is then applied, as discussed above, to allow purification of, or enrichment for, neural progenitor cells.

A number of genes that are differentially expressed in neural progenitor cells were known at the priority date, for example, Pax 3, Mash-1, Math-4a, Pax 6, GFAP, and Islet-1/2 (as recited in claim 76). At page 7 of the Office Action, the Examiner

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expresses a concern that these genes are expressed after the neural progenitor cells have been purified and enriched by Sox selection, rather than during the differentiation/selection process. This concern reflects a misunderstanding of the invention. As noted above, the claimed methods involves modification of pluripotent cells prior to induction of differentiation. The modified pluripotent cells are then induced to differentiate to generate neural progenitor cells or a population of cells comprising neural progenitor cells. Selection is then applied to purify, or enrich for, neural progenitor cells present in the differentiated culture. The genes specified in Claim 76 are, like the Sox genes, expressed in neural progenitor cells but not expressed in pluripotent cells (or are expressed in pluripotent cells at very low levels). Thus, the method can be carried out by inserting a selectable marker gene into a pluripotent cell under the control of the promoter of any gene that is differentially expressed in neural progenitor cells.

The specification exemplifies the selection of cells in which expression of the selectable marker was under the control of a Sox 2 promoter. The selected cells were confirmed to be neural progenitor cells by detecting expression of Pax 3, Delta-1, Mash-1, Math-4a, and Pax 6. (Page 12, lines 7-12.) However, the invention can be carried out equally well by introducing a selectable marker gene into a pluripotent cell so that the selectable marker is expressed under the control of, for example, the Pax 3 gene and by confirming the identity of the selected cells as neural progenitor cells by detecting expression of Sox genes.

The specification, therefore, provides sufficient guidance on how to carry out the invention using a selectable marker which is expressed under the control of a promoter

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of a gene that is differentially expressed in neural progenitor cells which is not a Sox gene, including the genes specified in Claim 76. This has been confirmed in the Declaration of Meng Li, filed in this application on June 19, 2003.

Finally, the Examiner has requested further explanation of the role of the stimulant, which is exemplified by retinoic acid in the specification, in carrying out the methods of the invention. Applicants respectfully submit that the Examiner has misunderstood the role of retinoic acid, believing it to directly stimulate the expression of Sox genes. This is not the case. Rather, the role of the stimulant is to induce pluripotent cells to differentiate down a neural lineage, or down a number of lineages, including one that leads to neural cells.

Any suitable stimulant may be used to induce differentiation of the pluripotent cells, and will result in a culture including neural progenitor cells expressing the same subset of genes, regardless of the specific stimulant used to induce the differentiation. Enrichment for, or purification of, the neural progenitor cells in the culture is then achieved by applying selection to the culture so that only those neural progenitor cells in which the selectable marker is differentially expressed survive. Thus, it is not essential to use retinoic acid to induce differentiation. Any stimulant of differentiation can be used so long as the population of differentiated cells derived from the original pluripotent cells includes some neural progenitor cells.

In view of the foregoing remarks, Applicants submit that this claimed invention is enabled by the specification. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims. Alternatively, Applicants submit that the entry of the

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amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

Applicants do not believe that any extensions of time are required to enter this response. However, in the event of an error, please grant any necessary extension and charge any required fee to deposit account 06-0916.

Respectfully submitted,

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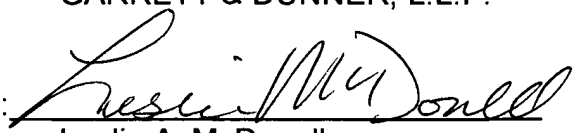
By: 

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